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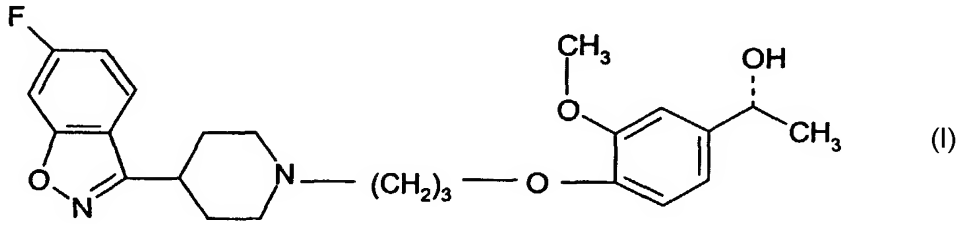
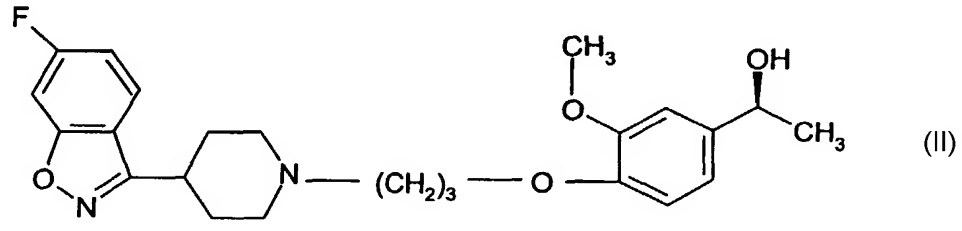
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OPTICAL ISOMERS OF AN ILOPERIDONE METABOLITE



(I)



(II)

(57) Abstract: The invention provides compounds of formulae (I) and (II), their preparation and their use as pharmaceuticals.

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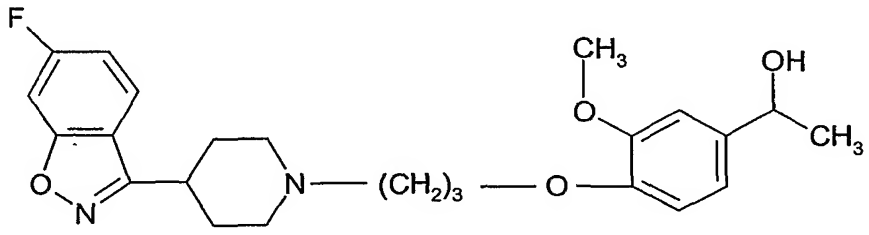
Optical isomers of an Iloperidone metabolite

The present invention relates to novel isomers of a metabolite of Iloperidone, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly, the invention relates to optical isomers of the metabolite P-88-8991 of Iloperidone.

Iloperidone is an atypical antipsychotic developed for the treatment of schizophrenia, having functional affinity for noradrenergic, dopaminergic and serotoninergic receptors. See for example Richelson E. and Souder T., Life Sciences, 68:29-39 (2000).

P-88-8991 is a major circulating metabolite of Iloperidone in human plasma, having the formula A

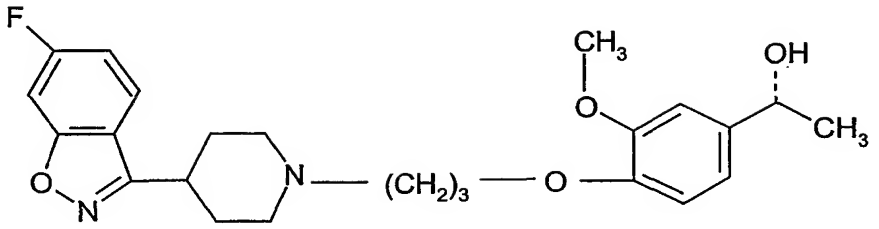


A

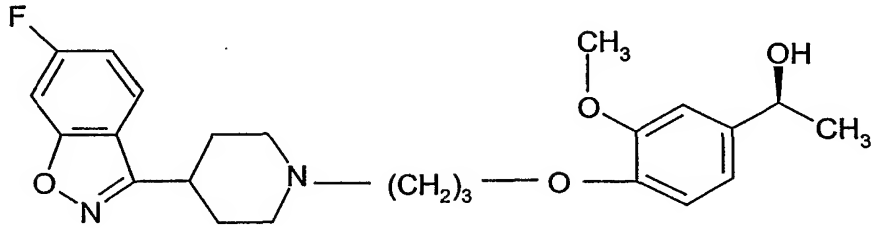
See for example Mutlib AE et al., Drug Metab. Dispos; 23(9):951-964 (1995). P-88-8991 has been shown to have plasma levels in human about 1.5 fold higher than the parent drug. It is roughly as active as Iloperidone.

P-88-8991 consists of a mixture of two enantiomers which have never been disclosed in the literature. It has now surprisingly been found that humans produce only one enantiomer stereospecifically following administration of Iloperidone.

In the first aspect, the invention provides the enantiomers (R)-P-88-8991 and (S)-P-88-8991 of formulae I and II



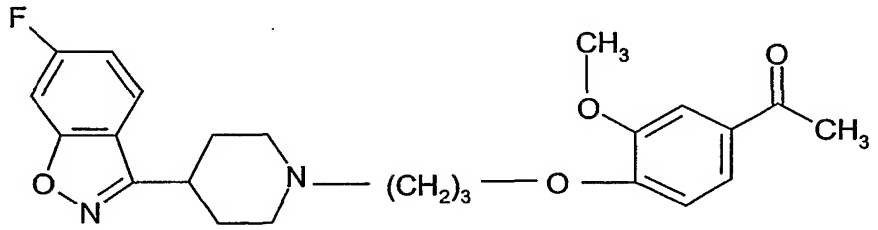
I



II

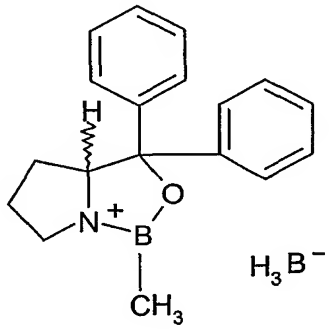
in free base or acid addition salt form.

In a further aspect, the invention provides a process for the production of the compounds of formulae I and II, comprising the reduction of Iloperidone of formula III



III

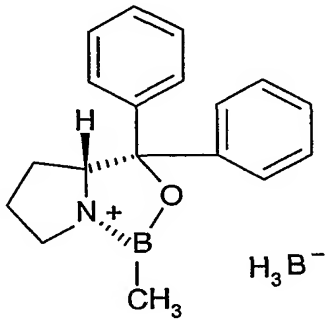
with an optically active boran complex of formula IV



IV

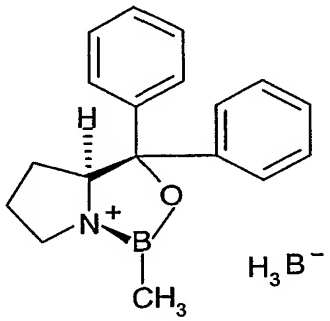
The compound (S)-1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol of formula I is obtained using the boran complex of (3aR, 7R)-1-

methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole of formula IVa



IVa

whereas the compound (R)-1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]propoxy}-3-methoxy-phenyl)-ethanol of formula II is obtained using the boran complex of (3aS,7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole of formula IVb



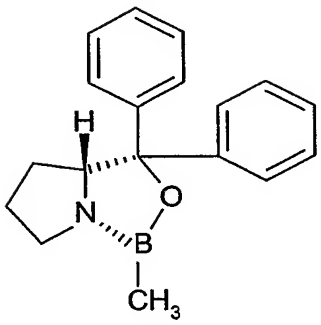
IVb

The reactions can be effected according to conventional methods, e.g. as described in the Examples.

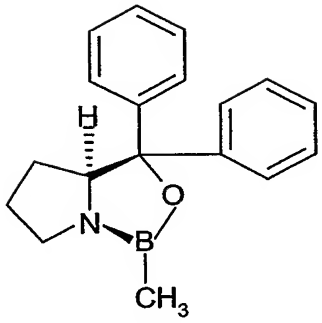
Working up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa. Suitable acid addition salts for use in accordance with the present invention include for example the hydrochloride.

The boran complexes used as starting materials can be produced from the corresponding compounds of formula Va and Vb



Va



Vb

according to known procedures, e.g. as described in the Examples.

The starting materials of formulae Va and Vb are known.

The compounds of formulae I and II and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular the agents of the invention display high affinity for adrenergic α_1 and α_{2c} receptors (pK_i 8.9 and 7.8 respectively, for the compound of formula I, and 9.2 and 7.7 respectively, for the compound of formula II), high affinity for 5 HT_{2A} and 5 HT_6 receptors (pK_i 8.9 and 8.1 respectively, for the compound of formula I, and 8.9 and 7.8 respectively, for the compound of formula II) and moderate affinity for the D_2 family (pK_i 7.4 to 7.6 for the compound of formula I and 7.4 to 7.8 for the compound of formula II).

Receptor affinity is determined with standard radioligand binding techniques, using human recombinant receptors and native rat brain receptors. Blockade of dopamine D_2 and noradrenergic α_{2c} receptors is tested in cell-lines using luciferase reporter gene assays based on 2nd messenger responses.

In vivo, the agents of the invention exhibit antipsychotic activity, as assessed in standard tests such as the amphetamine-induced hypermotility and the phencyclidine-induced hyperlocomotion tests.

The amphetamine-induced hypermotility test is performed according to the method described by Arnt J in Eur. J. Pharmacol. 283, 55-62 (1995). In this test, the agents of the invention significantly inhibit the amphetamine-induced locomotion of the animals at doses of

about 0.01 to about 10 mg/kg s.c.

The phencyclidine-induced hyperlocomotion test is performed according to a rat adaptation of the method described by Gleason SD and Shannon HE in Psychopharmacol. 129, 79-84 (1997). In this test, the agents of the invention significantly block the phencyclidine-induced hyperlocomotion of the rats at doses of about 0.01 to about 10 mg/kg s.c.

The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia and bipolar disorders.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 500, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The agents of the invention may alternatively be administered e.g. topically in the form of a cream, gel or the like, or by inhalation, e.g. in dry powder form.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of an agent of the invention. The composition may be buffered to a pH in the range of e.g. from 3.5 to 9.5, by a suitable buffer.

The agents of the invention can be administered either alone or in combination with other pharmaceutical agents effective in the treatment of psychotic disorders such as

schizophrenia or bipolar disorders. The present invention thus provides a combination comprising a therapeutically effective amount of an agent of the invention and a second drug substance, for simultaneous or sequential administration.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of psychotic disorders.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of psychotic disorders.

In still a further aspect the present invention provides a method for the treatment of psychotic disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Example 1

(S)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol

56.36 g of boran complex of (3aR, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole (1 equivalent) is dissolved under nitrogen in methylenchloride, and the solution is cooled to 0°C. A 1M solution of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone (iloperidone; 1 equivalent) in methylenchloride is added via a dropping funnel over 90 minutes while the internal temperature is maintained at 0°C ± 2°C. After the addition is complete, the mixture is stirred at 0°C for 20 hours. The reaction mixture is then poured into precooled methanol (0-5°C) during 1 hour. The solution is warmed to room temperature and stirred until the H_2 evolution ceases. The solution is concentrated by distillation and the residue dried in vacuum, treated with methanol and stirred for about 1 hour at 50°C and an additional hour at 0°C. The product is isolated by filtration and dried under reduced pressure for 3 hours at 50°C. The title compound is obtained (white crystals).

$[\alpha]_D^{20}$ – 19.3° (c=1 in chloroform)
Mp: 138.2 – 138.8°C

The boran complex used as starting material can be obtained as follows:

200 ml of a solution of (3aR, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole (1M in toluene) is stirred at room temperature under nitrogen. 1.2 equivalent borane-dimethylsulfide complex is added with a syringe. The solution is stirred for 2 further hours at room temperature. The borane complex is then crystallised by addition of 4 vol dry hexane and cooling to –12°C for 1.5 hour. The product is isolated by filtration in a sintered glass funnel and dried in vacuum at 40°C. The boran complex is obtained /white crystals).

Example 2

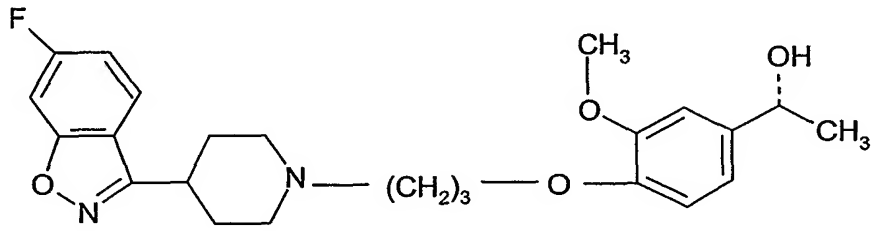
(R)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenlyl)-ethanol

This compound is produced in analogy to Example 1, using boran complex of (3aS, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole.

$[\alpha]_D^{20}$ = + 18.4° (c=1 in chloroform)
Mp: 137.9 – 138.3°C

CLAIMS

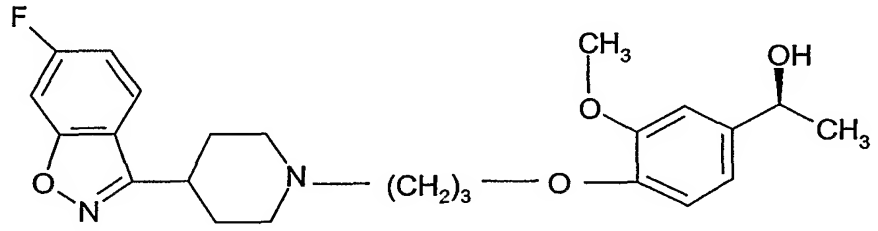
1. (R)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol of formula I



I

in free base or acid addition salt form.

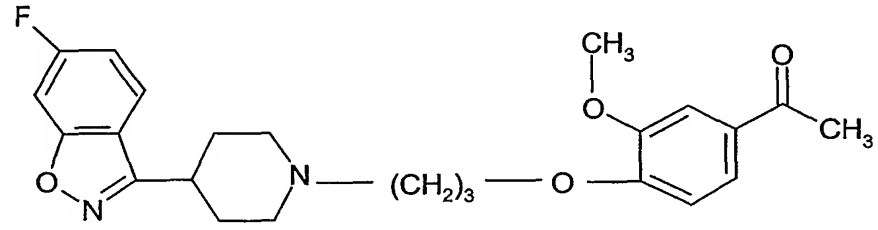
2. (S)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol of formula II



II

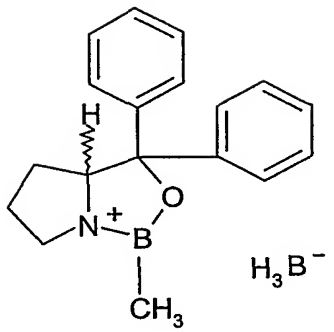
in free base or acid addition salt form.

3. A process for the production of the compounds of formulae I and II according to claims 1 and 2, and their salts, comprising the reduction of Iloperidone of formula III



III

with an optically active boran complex of formula IV



IV

and recovering the resulting compound in free base or acid addition salt form.

4. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

5. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic disorders.

6. A pharmaceutical composition comprising a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

7. The use of a compound of claim1 or 2 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of psychotic disorders.

8. The use of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic disorders.

9. A method for the treatment of psychotic disorders in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form.

10. A combination comprising a therapeutically effective amount of a compound of claim 1 or 2 in free base of pharmaceutically acceptable acid addition salt form, and a second drug substance, for simulataneous or sequential administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/09700

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D261/20 A61K31/42 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 402 644 A (HOECHST ROUSSEL PHARMA) 19 December 1990 (1990-12-19) page 27; example 9 ---	1-10
X,Y	STRUPCZEWSKI J T ET AL: "3-(ARYLOXY)ALKYLPIPERIDINYL-1,2-BENZISOXAZOLES AS D2/5-HT2 ANTAGONISTS WITH POTENTIAL ATYPICAL ANTIPSYCHOTIC ACTIVITY: ANTIPSYCHOTIC PROFILE OF ILOPERIDONE (HP 873)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 7, 1995, pages 1119-1131, XP000941571 ISSN: 0022-2623 table 3, entry 56 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2002	06/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MUTLIB A E ET AL: "Picogram determination of iloperidone in human plasma by solid-phase extraction and by high-performance liquid chromatography-selected-ion monitoring electrospray mass spectrometry" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL APPLICATIONS, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 669, no. 2, 21 July 1995 (1995-07-21), pages 237-246, XP004043810 ISSN: 0378-4347 abstract	1,2
Y	COREY E J ET AL: "A STABLE AND EASILY PREPARED CATALYST FOR THE ENANTIOSELECTIVE REDUCTION OF KETONES. APPLICATIONS TO MULTISTEP SYNTHESES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 109, no. 25, 8 December 1987 (1987-12-08), pages 7925-7926, XP000652664 ISSN: 0002-7863 the whole document	3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/09700

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